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Supplementary Material

Appendix 3 Safety and Validity Evaluation

HIV 免疫基因 CCR5 胚胎基因编辑安全性和有效性评估

Safety and validity evaluation of HIV immune gene CCR5 gene editing in human embryos

研究目的

HIV 导致的 AIDS 是的当今世界威胁全人类的一大医学难题，影响着全人类的生命安全和身体健康。迄今为止，没有有效的药物或临床技术手段可完全治愈 AIDS。所幸全世界各国政府和科学家投入大量精力做 HIV 预防和感染后干预，但是距离 WHO 关于 2020 年 HIV 防治目标任然很远，距离消除 HIV 任重道远。迄今为止唯一一例全世界被公认完全治愈的 HIV 感染者是“柏林病人”，当时患者出现白血病，在做骨髓干细胞移植前检查出为 HIV 阳性感染者，德国医生采用了一个西欧人群中罕见可以抵御 HIV-1 的基因突变-具有 CCR5 突变的骨髓配型的创造性的治疗了该患者的白血病，同时到今天为止“柏林病人”的体内已检测不到 HIV 病毒，为消灭 HIV 创造了新的医疗模式。本试验在细胞系、动物实验和人类废弃胚胎的基础上，招募罹患不孕不症的 HIV 阳性患者，通过充分的知情同意告知志愿者风险及获益，通过一对一面谈，签署知情同意书；同时提交合作医院伦理委员会讨论并通过实验设计。通过 CCR5 基因编辑人类胚胎，通过完善的试验体系，获得避免 HIV 健康小孩，为未来在人类早期胚胎彻底消除重大遗传疾病提供了新见解。

Purpose of Study

HIV-induced AIDS is a major medical problem that threatens all human beings in today's world, affecting the safety and health of all human beings. To date, there is no effective drug or clinical technique to completely cure AIDS. Fortunately, governments and scientists around the world have invested a lot of energy in HIV prevention and post-infection interventions. However, we are far from achieving the WHO's 2020 HIV prevention goals and have a long way to go to eliminate HIV. The only HIV-infected person who has been recognized as completely cured in the world is the “Berlin patient”. At that time, the patient developed leukemia and was diagnosed as HIV-positive before the bone marrow stem cell transplant. The German doctor used a bone marrow matching to creatively treats leukemia in this patient with a rare CCR5 genetic mutation existing in Western European population resistant to HIV-1. To date, "Berlin patient" has not detected with HIV in the body, creating a new medical model for HIV elimination. The current clinical trial is based on preclinical research of cell lines, animal models and human waste embryos. It recruits HIV-positive patients with infertility and informs the volunteers of the risks and benefits through sufficient informed consenting. The informed consent form is signed

through one-on-one discussion. The study design was submitted to the ethics committee of the hospital for discussion and approval. Through the CCR5 gene editing of the human embryo in a comprehensive test system, we set to obtain healthy children to avoid HIV providing new insights for the future elimination of major genetic diseases in early human embryos.

纳入标准

生活在中华人民共和国的已婚夫妇艾滋病毒血清阳性（女性阴性，男性阳性）

男女 22–38 岁

男性临床稳定，检测不到病毒载量血症<75 拷贝/ mL;筛选时 CD4 计数> 250;至少在过去 12 个月内有连续抗逆转录病毒疗法的历史

临床证实满足试管婴儿（IVF）医学指针

受试者双方的充分知情同意，理解本试验目的、风险和利益

受试者双方都愿意承诺在卵子收集前和出生后一个月内使用预防性避孕或保持禁欲至少两个月

Inclusion Criteria

1. Married couple living in the People's Republic of China with HIV seropositivity (female negative, male positive);

2. Men and women 22–38 years old;

3. Males are clinically stable, failing to detect viral load of <75 copies/mL; screening for CD4 counts > 250; at least in the past 12 months with a history of continuous antiretroviral therapy;

4. Clinically confirmed to meet the medical guidelines for IVF therapy;

5. Fully informed consent of the couple to understand the purpose, risks and benefits of the trial;

6. Both subjects are willing to commit to using preventive contraception or maintaining abstinence for at least two months before egg collection and within one month after birth.

排除标准

父亲在精子收集前可检测到的病毒载量> 75 拷贝/ mL

母亲或父亲在 CRISPR / Cas9 基因编辑的靶序列内具有遗传变异

母亲或父亲都有遗传变异，为 CCR5 靶向基因编辑创造了一种新颖的、高概率的脱靶位

点

在该研究期间，在两次卵母细胞取出周期后自然怀孕或受精失败

先前多次(IVF)体外受精尝试失败

禁忌使用孕期禁忌药品

患有内分泌相关疾病，性激素处于异常水平

目前用使用放化疗药物治疗肿瘤相关疾病的

参与或最近参加了另一项使用研究性诊断测试，药物或设备的临床试验

患有疾病的受试者，包括酒精滥用或精神疾病，可能会导致研究人员或临床医师的判断而影响研究方案

Exclusion Criteria

1. The viral load of the father before sperm collection is > 75 copies / mL;

2. Mother or father has genetic variation within the target sequence of the CRISPR/Cas9 gene editing;

3. Mother or father has genetic variation, creating a novel, high-probability off-target site for CCR5-targeted gene editing;

4. During the study, natural pregnancy or fertilization failed after two oocyte stimulation cycles;

5. Previously multiple in vitro fertilization (IVF) attempts failed;

6. Contraindications to use drugs during pregnancy;

7. With endocrine-related diseases, sexual hormones are at abnormal levels;

8. Currently using chemoradiotherapy drugs to treat tumor-related diseases;

9. Participated in or recently participated in another clinical trial using a research diagnostic test, drug or device;

10. Subjects with other diseases, including alcohol abuse or mental illness, that may influence the current protocol based on the researcher or clinician's judgment.

测量指标

怀孕并保证一个或多个活产

Pregnancy and guarantee one or more live births

亲代和子代全基因组深度测序分析

Father, mother and progeny genome-wide deep sequencing analysis

随机方法

HIV 公益组织派发问卷调查，寻找满足条件志愿者，入组面谈，医疗结构体检，签署知情同意书随机入组

Randomization Procedure

AIDS public welfare organizations randomly distributes questionnaires to find qualified volunteers, recruitment interviews, medical examinations at hospitals, and signing informed consent.

数据采集和管理

一为病例记录表(Case Record Form, CRF)，二为电子采集和管理系统(Electronic Data Capture, EDC)，试验结束 6 个月后提供网址和数据

Data Collection and Management

Clinical trial data will be collected using the case report form (CRF). The data will be managed by an electronic data capture (EDC) system. Results will be reported 6 months after the study completes.

Online Registration:

http://www.chictr.org.cn/showproj.aspx?proj=32758

ChiCTR1800019378